REMARKS

Status of Claims

Claims 11, 38 and 57-59 are cancelled.

Claims 1-10, 12-37, 39-56, 60 and 61 are pending.

Claim 61 is now indicated as being "withdrawn".

Accordingly, claims 1, 3, 8, 12, 14, 20, 21, 30-37, 39-56, 60 and 61 are withdrawn from examination.

Claims 2, 4-7, 9, 10, 13, 15-19, and 22-29 are presented for examination on the merits.

All claims have been amended to replace the lower limit of a 5 nucleotide fragment of a DNA gene or gene segment specific for sepsis and/or sepsis-like conditions, for use in hybridization to test for presence and levels of complementary RNA, with a lower limit of 20 nucleotides, as supported e.g. by paragraph [0102] of the specification as filed.

Election/Restriction

The Examiner maintains the restriction requirement for the reason that "the common technical feature" (use of body fluids for measurement of gene expression profiles) alleged by Applicants is not a special technical feature.

Applicants respectfully traverse.

The "use of body fluids" was used by Applicants to show that Chinnaiyan does not teach all features of the independent claims. The Anderson reference newly cited by the Examiner may show "body fluids"; however, Anderson does not teach the remaining inventive features of the broad inventive claims. The two references can not be combined and even if read together do not teach all features of the independent claims. Thus, the present broad claims do have a common technical feature not disclosed in the prior art. Accordingly, withdrawal of the restriction requirement is proper.

More specifically, the Examiner originally based the "lack of common technical feature" on Chinnaiyan et al (cited in the WO Lack of Unity of Invention determination) for

teaching sacrificing a rat and harvesting ***tissue*** samples to monitor progression of gene regulation of infected rats during the course of sepsis.

Applicants distinguished the present invention from Chinnaiyan by pointing out that the present claims are directed to testing a sample of a body fluid to perform a diagnostic test in order to allow early (prior to onset of clinical symptoms) diagnosis and treatment of obviously live humans. Thus all, the claims had a common technical feature not disclosed in Chinnaiyan et al.

The Examiner now cites a new reference, Anderson et al US PG Pub 2003/0194752 A1 (publication of 10/400,275, with priority to the filing on 04/02/2002) as providing for teaching the quantitative analysis of marker biomolecules from body fluids, and takes the position that the present claims have no special common technical feature novel over Anderson.

Applicants traverse this new basis for finding of lack of unity of invention.

Anderson notes that various biological markers fluctuate over time within the same individual, and proposes a diagnostic test involving ***monitoring these fluctuations over time*** and independently deriving for each marker a marker statistic that is a statistical measure of extreme value of said marker over said period of time.

In the present invention, in contrast, only one sample need be taken from the patient to carry out diagnosis, and it is compared against a non-pathogenic sample, i.e., from a healthy individual. Diagnosis is rapid; it is not necessary to monitor the patient and take multiple samples over days to arrive at a diagnosis.

As all pending claims have in common this single-sample diagnosis, a special technical feature not disclosed in Anderson, all claims have unity of invention.

More specifically, as explained in paragraph [0026] of the present application as published, the point of origin of the present invention is the realization that ***RNA levels different from normal values***, respectively peptide levels or peptide segment levels derivable from the RNA levels, that can be detected in a serum or plasma of a patient whose risk is high that he will be suffering from SIRS, or who suffers from symptoms that are typical for SIRS,

can be detected before SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections are detected in biological samples.

Anderson et al in contrast teaches a rather lengthy procedure comprising

a) ***monitoring*** a plurality of biological markers in the same individual ***over a period of time***,

b) independently deriving for each marker a marker statistic that is a statistical measure of extreme value of said marker over said period of time, and

c) applying a decision rule to the marker statistics from step (b) to detect early sepsis in said patient. The marker statistic may be maximum, minimum, maximum percent increase, minimum percent increase, maximum percent decrease, and minimum percent decrease, maximum time spent either above or below a threshold, minimum time spent either above or below a threshold, maximum level of variability, and minimum level of variability. The plurality of markers may be selected from leukocyte count, cell surface markers, soluble markers, markers of a pro-inflammatory response and markers of a compensatory anti-inflammatory response.

Only in claims 57-59 and paragraph [0069] of Anderson is there the merest mention that the tests can be carried out using RNA and DNA molecules that encode protein markers. There is however no teaching which precise RNA or DNA molecules may be used. There are no working examples in the specification actually using RNA or DNA molecules. There is no teaching how in practice to test using RNA or DNA molecules. In fact, levels of RNA are continuously varying over time in a live cell, thus there is no explanation of how to correlate fluctuating RNA levels with diagnosis of specific conditions. Thus, the specification is non-enabling for ***monitoring fluctuations in*** RNA or DNA molecules ***over time***, much less for a single-sample based diagnosis.

Since all independent claims have the same linking common technical feature which is not disclosed in the prior art, and since unity of invention has been established by the above explanation, claims 1, 3, 8, and 14, at a minimum (quantifying gene levels in body fluid

samples), should be rejoined, and in fairness all claims (including claims 30-56 directed to quantifying protein levels of body fluid samples) should be under examination as being directed to the same generic invention.

Claim Objections

*Claim 2 continues to be objected to over recitation of the phrase 'isolating **of** sample RNA from a sample of a mammal', where the phrase 'isolating sample RNA from a sample from a mammal' is correct.*

In response, Applicants submit that the word "of" had previously been deleted by "strike through" in the Amendment A filed August 31, 2009. Apparently, the computer did not register this deletion. Applicants now present claim 2 as amended to delete the word "of". Entry of this as-amended claim 2 is respectfully requested.

New Claim Objections

Claim 61 is objected to for the specific recitation of non-elected subject matter.

In response, Applicants first refer the Examiner to the above traversal of the lack of unity of invention rejection. It is respectfully submitted that all claims are directed to the same invention: the discovery that ***RNA levels different from normal values***, or peptide levels or peptide segment levels derivable from the RNA levels, that can be detected in a serum or plasma of a patient whose risk is high that he will be suffering from SIRS, or who suffers from symptoms that are typical for SIRS, can be detected before manifestation of clinical symptoms of SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections.

Applicants appreciate the Examiner's indication that upon allowance of a claim directed to the elected invention, the Examiner will consider rejoinder of the subject matter of the non-elected combinations, and rejoinder of any combinations that include all of the limitations of the allowed elected subcombination. Prior to allowance, any non-elected subject

matter that is not re-joined with the elected subject matter will be required to be removed from the claims.

Applicants accordingly, for the present, amend the status identifier of claim 61 as "withdrawn", but look forward to rejoinder.

New Claim Rejections - 35 USC § 112 2nd ¶ Indefiniteness

Claims 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is unclear over recitation of the phrase 'the immobilized probes' because there is a lack of sufficient antecedent basis for any 'immobilized probes'.

In response, Applicants have corrected the dependency of this claim to depend from claim 7.

Claim 27 is unclear over recitation of the phrase 'the cDNA probes' because there is a lack of sufficient antecedent basis for any `cDNA probes'.

In response, Applicants have corrected the dependency of this claim to depend from claim 15, and have deleted the unnecessary term "probes".

Claim 28 and 29 are unclear over recitation of the phrase 'the individual cDNA molecules' because there is a lack of sufficient antecedent basis for any 'individual molecules' probes'.

In response, Applicants have corrected the dependency of these claims to depend from claim 15, and have also changed "the carrier material" to "a carrier material", and further, have removed the "and/or" language.

Maintained Claim Rejections - 35 USC § 112 1st - Written Description Newly Applied to Claims as Necessitated by Amendments

Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of claims for lack of adequate written description is relevant to the rejected claims, drawn to methods for in vitro diagnosis of sepsis and/or sepsis-like condition, as they require RNA or DNA 'being a gene or gene fragment specific for sepsis' (as recited in independent claims 2 and 13), and encompassing ***'gene fragments thereof with' as few as 5 nucleotides*** *(as recited and encompassed by claims 13 and 61). In the instant case the specification does not provide the skilled artisan with written description that adequately identifies characteristics of particular nucleic acids suitable for performing the claimed method as generically encompassed by the claims (i.e. the claims generically require nucleic acids with the functionality of being 'specific for sepsis') as well as methods requiring* ***minimally 5 nucleotides*** *of the sequences recited in claims 13 and 61.*

In response, Applicants have amended all claims to require that the probe comprise a minimum of 20 nucleotides. A 20 nucleotide sequence fragment of DNA is adequate for purposes of detection and quantification of specific RNA.

That is, there is no requirement that the DNA have any functionality other than that it hybridize with the target RNA. For successful detection of target RNA, all that is required is that the DNA fragment be (a) from a gene specific for sepsis or sepsis like conidtion and (b) of a sufficient length so that hybridization with RNA from a patient is reasonably expected to be indicative of a "match" between the DNA and RNA. While, as pointed out by the Examiner, 5 base pair match may or may not be an adequately specific indicator, a 20 base pair match would be sufficiently selective and indicative of a match.

The Examiner further indicates that, while the specification asserts that there is a group of genes from humans that are differentially expressed in humans with sepsis as

compared to a non-septic individual (i.e. Tables 8 and 9), there is no disclosed relationship between the ***structure*** *of the genes (i.e. their nucleotide sequences) and their* ***functionality*** *(i.e. diagnostic of sepsis) such that the skilled artisan would recognize that Applicants are in possession of the methods as generically claimed which encompass the use of any gene or fragment thereof. This is also relevant to the breadth of claims 13 and 61, which, consonant with the election, which encompasses any genes comprising* ***as few as 5 nucleotides*** *of the mRNA sequences as elected.*

In response, Applicants point out that the claimed diagnostic test involves detecting in a sample of body fluid from a patient level(s) of RNA which hybridize with DNA gene or gene fragment specific for sepsis, and comparing this against the level(s) of RNA in the control sample taken from a non-pathogenic human. There is no fractionation of RNA, and thus no requirement that a fraction of RNA have functionality. On the other hand, the probe used to measure the level of RNA, i.e., the DNA gene or gene fragment, is required to be, or be derived from, a gene specific for sepsis. The DNA may be a fragment as small as 20 nucleotides. It is not required that this DNA fragment have any particular structure, merely that it be from a DNA gene or gene fragment specific for sepsis, so that it can be used as a probe for detection of levels of complementary RNA.

Finally, the Examiner concludes that the specification, while providing a written description of methods requiring the step of, for example:

> *Comparing the abundance of particular mRNA species from a sample to the abundance of the same mRNA species from a control sample, wherein the mRNA species comprise SEQ ID NOs: 220, 303, 529, 754, 844, 1705, 2370, 2449, 2468, 2481, 2709, 2831, 2928, 2948, 3068, 3079, 3209, 3268, 3305, 3317, 3331, 3399, 3424, 3433, 3482, 3508, 3523, 3624, 3676, 3765, 3796, 3873, 3879, 3881, 3917, 4060, 4096, 4122, 4141, 4268, 4328, 4450, 4528, 4609, 4654, 4695, 4705, 4937, 5265, 5338, 5418, 5542, 5567, 5647, 5779, 6018 and 6200,*

it does not provide adequate written description of the broadly claimed (5 nucleotide probe) subject matter.

In response, Applicants submit that for detection of presence and levels of specific RNA by hybridization with DNA, it is not necessary that the entire DNA strand complementary to the RNA be used. Rather, all that is required is that a sufficient length of fragment of DNA be used so that the hybridization between the DNA fragment and the RNA can be expected to be indicative of the presence of the target RNA. A 20 base pair match between DNA and RNA is indicative of a DNA - RNA match.

Accordingly, in view of the amendments to the claims, withdrawal of the rejection is respectfully requested.

Response to Remarks

Applicants appreciate the Examiner's detailed feedback to the arguments presented in Amendment A.

With regard to the argument that the specification sets forth Tables 2, 3, 8 and 9 which provide the sequences of cDNAs significantly overexpressed and underexpressed, and indicative of SIRS, the examiner maintains that the disclosure of particular specific genes in a sample from a SIRS patient is not adequate to provide a description of the generically claimed methods that encompass the analysis of ***any gene*** *from the human genome.*

In response, Applicants point out that (a) the claims recite "wherein the DNA is a gene or gene fragment specific for sepsis and/or sepsis-like conditions", (b) the specification gives numerous examples of such genes, and (c) it is well within the skill of the person working in this art, given the disclosure of the present specification, to identify and add additional genes to the already lengthy list of identified genes.

Applicant respectfully point out that MPEP §2163 "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, para. 1, "Written Description Requirement" provides that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting

evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"). The Examiner has not met this burden.

Further, the MPEP provides "It is true that reduction to practice ordinarily provides the best evidence that an invention is complete." Applicant have provided ample examples demonstrating that they have completed the invention and were in possession of the invention at the time the application was filed. Accordingly, the Examples in the present specification demonstrate possession of the invention.

Further, "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem*, 323 F.3d at 963, 63 USPQ2d at 1613. An application specification may show actual reduction to practice by describing testing of the claimed invention ..."

Applicants further respectfully submit that the test of "undue experimentation" does not require either (1) *a priori* determination of results, or (2) minimal experimentation.

In *United States v. Telectonics Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied* , 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue

experimentation.

The question is (a) whether one of ordinary skill, having the teaching of the present invention, is reasonably enabled to practice the present invention, without undue experimentation, and (b) whether the claims *define* the scope of the invention with sufficient precision and clarity that those working in this art will be able to appreciate when they are within and outside the boundaries of the claims.

The Court in *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

Applicants respectfully submit that for the USPTO to grant, in exchange for a full disclosure of a valuable invention, protection limited only to specific disclosed representative sequences unfairly deprives inventors the protection they deserve, would take years of additional work given the long reproductive cycle of agricultural plants, and furthermore, ignores the advances in the art and the high level of skill of those working in this art.

Applicants respectfully submit that the specification, at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The Examiner next points out that claims requiring minimally 5 nucleotide of the recited sequences of claims 13 and 61 could be e.g. TTTTT, which would not be a probe specifically for RNA indicative of sepsis.

In response, Applicants point out that the claims have been amended to recite that the DNA fragment specific for sepsis be at least 20 nucleotides.

Maintained Claim Rejections - 35 USC § 112 1st ¶ Enablement
Newly Applied to Claims as Necessitated by Amendments

Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse. Hybridization is well known, a listing of genes indicative of sepsis are set forth in the specification, the ability to identify additional genes is within the skill of the person working in this art, it is not necessary that EVERY gene indicative of sepsis be identified, thus the present specification is sufficiently enabling.

Applicants are aware that under the precedent of *Regents of the University of California v. Eli Lilly,* 119 F.3d 1559 (Fed. Cir. 1997) and its progeny, there has evolved a detailed written description requirement for chemical and biotechnology patents separate and distinct from what is required under enablement. *Eli Lilly* involved claims directed to DNA sequences for encoding vertebrate and mammalian insulin. The specification

- identified (only) rat insulin DNA and
- a general method for isolating human DNA, which incorporated the method used to obtain the rat DNA.

Although the specification was arguably enabling for the broad claims, the Federal Circuit held that such a description was insufficient to describe human DNA as well as claims relating to broad genera of vertebrate and mammalian insulin DNA. The Court applied the written description requirement to claims that had no new matter. Compounding the already controversial decision, the panel singled out chemical and biotechnology patents by requiring that the written description provide "a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Another issue that has evolved under the (super)written description requirement is that a genus is not adequately described by reference to a small number of species. Thus, even where a specification provides enablement and detailed descriptions of representative species, the patent drafter must ensure that the species descriptions cover the full breadth of the claims. In litigation, whenever a claim is construed to cover more than just the examples described in the specification, it is vulnerable to a written description challenge. Accused infringers have used "lack of written description" as an expedient tool to invalidate patents on summary judgment.

In many cases, however, particularly with respect to DNA and proteins, the CAFC and the PTO have applied the requirement in a manner that is more demanding than enablement, effectively rendering it a ***super-enablement requirement***.

In re Wallach, 378 F.3d 1330 (Fed. Cir. 2004) provides an example of the species possession requirement being applied as a super-enablement requirement. In *Wallach,* the species possession requirement denied patent protection to an inventor who had discovered, described and apparently enabled a novel and useful DNA sequence. *Wallach* offered no policy rationale for requiring more than an enabling disclosure for DNA claims.

Today, twelve years after *Lilly* was decided, the CAFC has yet to articulate a cohesive statement of the standard for satisfying the species possession requirement, and has applied it in an inconsistent manner to arrive at irreconcilable outcomes for analogous inventions. In view of the lack of clarity and guidance from the CAFC, it is not surprising that the PTO has struggled in its attempts to interpret and apply *Lilly* and its progeny outside of the specific facts of those cases. As noted above, the heightened disclosure requirement of *Wallach* has not been applied to closely analogous biotechnological inventions involving antibodies and viral genomes.

In 2008, the PTO issued the revised Training Materials which replaced and superseded the earlier guidelines. In many cases, the original and 2008 versions arrive at entirely different conclusions with respect to the patentability of essentially identical claims and specifications, as explained in detail on Holman's Biotech IP Blog. The deep confusion and inconsistency at the PTO is symptomatic of the fundamental flaws in the doctrine itself.

For example, the USPTO's own current Written Description Training Materials (conclude that a broad genus claim reciting an "isolated antibody capable of binding to [a protein identified as] antigen X" satisfies the written description requirement, even though the specification indicates that not one single antibody falling within the scope of the claim has ever been made, and provides no description of the structural, physical or chemical properties of any antibody falling within the scope of the claim. Training Materials Example 13.

Attempts by the PTO to justify the discrepancy merely serves to illustrate the illogic and unworkability of the species possession requirement, and super written description requirement in general.

In April 2009, the controversy over the written description requirement continued in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 560 F.3d 1366 (Fed. Cir. 2009). In that case, the Federal Circuit invalidated claims on written description grounds without discussing enablement. However, it appeared that the Court had difficulty coming up with some explanation as to why the disclosure of some structures, coupled with the description of how to use those structures, failed to provide adequate description. While Ariad claims might be too broad, it becomes apparent to the reader that enablement is the actual concern, and the correct tool for policing claim scope. In a concurrence, Judge Linn stated that the Court's "*engrafting of a separate written description requirement onto section 112, paragraph 1 is* ***misguided***." Using Judge Linn's statements for support, the patentee in *Ariad* requested a rehearing *en banc* on the issue. On August 21, 2009, the Federal Circuit granted the patentee's request. The Court requested additional briefing on two issues:

(i) **whether the first paragraph of section 112 contains a written description requirement separate from an enablement requirement**; and

(ii) if a separate written description requirement is set forth in the statute, the scope and purpose of the requirement.

This foretells that the Court is opening the door to reconsidering and revising the "super" written description requirement it set forth in *Eli Lilly*. Applicants respectfully request the

Examiner to decide the issue of enablement not under the faulty standard of *Eli Lilly* but to await new guidance expected under *Ariad*. Applicants believe that the Federal Circuit will dismiss the separate written description requirement. An enabling description of a method for isolating the sequence, and a few detailed examples (species), as presently disclosed, should then be held adequate to support generic claims.

Nature of the invention and breadth of the claims

The claims are drawn to methods of diagnosis of sepsis and/or sepsis like conditions in human.

The claims generically encompass analysis of any gene or fragment ***specific for sepsis****.*

According to the Examiner, the claims encompass any comparison of any labeled RNA, as well as any fragments of the elected combination of SEQ ID NOs, or fragments minimally comprising 5 nucleotides of the recited SEQ ID NOs.

In response, Applicants point out that the claims have been amended to require a minimum of 20 nucleotides. Hybridization thus would give a high probability of detection and level of target RNA.

According to the Examiner, the claims encompass detection of any condition that can be considered `sepsis-like condition'.

In response, Applicants point out that the claims require the use of "at least one DNA being a gene or gene fragment ***specific for sepsis***". Thus, the test is specific. A positive test result is to be interpreted as indicative of sepsis, or could also be indicative of a sepsis like condition.

According to the Examiner, the claims thus require knowledge of a correlative association between any expression levels of a wide variety of RNA combinations and a variety of different phenotypes in different subjects.

In response, Applicants respectfully point out that the essence of the present invention is the discovery that RNA levels can be an early indicator of the progress of sepsis, allowing diagnosis and treatment before clinical symptoms are manifest. This is the "invention" that must be described in the specification. It is not necessary that EVERY gene and every fragment of every gene be set forth in the specification. It is sufficient that a representative number of genes be set forth such that a person of ordinary skill could, without undue experimentation, identify additional genes if desired.

Thus, the invention of a diagnostic test allowing an early diagnosis of sepsis – the essence of the invention – is adequately explained and enabled by the present specification.

Direction provided by the specification and working example

Relevant to the Election, the instant specification provides a comparative analysis (Example 3 — p.26) of gene expression in two human individuals, one classified as a sepsis patient and the other classified as a non-septic control subject (Table 7). The specification provides that 54 particular genes were over-expressed in the sepsis-patient sample (Table 8), and 56 particular genes were under-expressed in the sepsis-patient sample (Table 9). Relevant to the claims and the elected invention, the specification provides the aforementioned analysis of sepsis gene expression, but does not provide for gene expression in the generic 'sepsis-like conditions'.

In response, Applicants point out that the claims require the use of "at least one DNA being a gene or gene fragment ***specific for sepsis***". Thus, the test *per se* is specific. However, a positive test result not necessarily always indicative of sepsis, it could also be indicative of a sepsis like condition. Accordingly, the claim and test are precise, and the fact that the results may indicate conditions incidental to sepsis does not render the claims indefinite.

Further, Applicants respectfully point out that the specification teaches (Abstract and paragraph [0120]) that the invention is applicable to sepsis-like systemic inflammatory

conditions and sepsis-like systemic infections. These more specific conditions which are closely related to sepsis have now been incorporated into the claims.

According to the Examiner, the specification provides only the results of a comparison between two individual subjects (a single case and a single control), with no validation of the asserted particular mRNAs specific for sepsis, nor any analyses of populations of cases or controls. There is no statistical analysis of the reliability of classification using expression of particular mRNA species.

In response, Applicants point out that the specification need not meet the level of a defensible thesis, or prove reproducibility of results. All that is necessary is that the specification show that the inventor appreciated the invention, and that the specification teach those working in the art to make and use the invention.

Additionally it is noted that the particular mRNAs asserted in the specification are not included in the mRNAs of the Election.

In response, Applicants submit that the specification as a whole teaches, shows possession of, and enables the generic invention. Withdrawal of the election of species requirement and consideration of the generic invention is respectfully requested.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the abundance of any particular nucleic acid biomarker or combination of biomarkers is high, the unpredictability associated with correlating any comparison of abundances with a particular phenotype such as sepsis, is even higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Because the claims encompass comparing any abundances of any particular RNAs to any control RNAs, where the specification provides only the example of analysis of two individuals (one case and one control), it is relevant to point out the unpredictability in using gene expression to establish a phenotype.

In response, Applicants point out that not all experimentation need be set forth in the specification in order to show possession of the invention and to enable those working in the art to reproduce the invention.

Because claims encompass the analysis of gene expression in any body fluid, whereas the specification provides only expression in whole blood samples, it is relevant to point out the unpredictability in comparing gene expression among different tissues. Cobb et al (2002) teaches the unpredictability in analysis of gene expression different tissue sample types of a septic mammal, specifically in spleen and liver samples from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., Ins.2-8).

In response, Applicants point out that the present body fluid samples are taken from a human clinical patient. It is logical and preferred to take a blood sample; however, the invention is not limited to blood samples.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to establish that any level of nucleic acid abundance of any RNAs (as generically encompassed by the claims), as compared to a control, is indicative of sepsis. Such experimentation would require case:control analysis of a population large enough to attain statistical significance, and require the analysis of different tissue types and analysis of any RNA species of interest. Even for the particularly elected SEQ ID NOs it is noted that the instant specification does not provide that these mRNAs are robustly and reliably diagnostic of the presence of sepsis or any other condition that may be considered 'sepsis-like', nor does the specification provide that ***RNA minimally comprising 5 nucleotides*** *of the recited RNAs, as encompassed by the claims, may be used in a method of sepsis diagnosis.*

Applicants respectfully traverse, particularly in view of the amendment of the claims to require a minimum of a 20 nucleotide DNA sequence as the hybridization probe.

Given the present art, "reasonable experimentation" may be time consuming and expensive. In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of ***time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation.***

Accordingly, it being well within the ability of those working in this art, given the teaching of the present specification, to expand the list of genes with which the invention can be carried out, withdrawal of the rejection and indication of allowance is respectfully requested.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement.

Applicants have argued that the claims have been amended to recite genes for which a written description is provided. The argument is not persuasive as the Examiner maintains that the claims still encompass methods which are generic with regard to the RNA species required for analysis in the diagnosis of sepsis, and the claims still broadly encompass RNA species minimally comprising 5 nucleotides of the recited particular sequences.

Applicants have additionally argued that 'sepsis-like' conditions are typically recognized in a clinical setting by evaluation of subjective criteria. The Examiner maintains that the claims do not require, nor does the specification provide, any limiting definition for 'sepsis-like' conditions. As such the claims are sufficiently broad to encompass anything

reasonably considered to be 'sepsis- like', where phenotypes as diverse as fever, inflammation, and increased heart rate may be considered 'sepsis-like' as they may be components of sepsis.

In response, Applicants point out that the claims are specific in that they require that a specific test be carried out – hybridization of RNA with "at least one DNA being a gene or gene fragment specific for sepsis". Thus, the test per se is specific. However, a positive test result not necessarily always indicative of sepsis, it could also be indicative of a sepsis like condition. Accordingly, the claim and test are precise, and the fact that a positive diagnosis may indicate conditions incidental to sepsis does not render the claims indefinite.

Further, Applicants respectfully point out that the specification teaches (Abstract and paragraph [0120]) that the invention is applicable to sepsis-like systemic inflammatory conditions and sepsis-like systemic infections. These more specific conditions which are closely related to sepsis have now been incorporated into the claims.

Finally, Applicants have argued that "the specification provides highly statistically relevant correlation between gene expression and condition of sepsis" (p.55 of Remarks). However, the Examiner maintains that while the specification may show large differences in measures of gene expression, the specification in fact provides only the analysis of a single case and a single control subject. There is no validation of the asserted association, where given the teachings of the art cited by the Examiner to demonstrate the unpredictability of gene expression association studies, the Examiner maintains that it is unpredictable as to whether or not the associations asserted in the specification would hold true for any other individual subject or populations in general.

In response, Applicants maintain that the teaching is sufficiently representative and enabling. The underlying principle is sound and reasonable. The hybridization test is not a matter of chance but is well established.

Withdrawal of the rejection is respectfully requested.

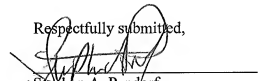
Withdrawn Claim Rejections - 35 USC § 102

Applicants appreciate the withdrawal of the rejection of claims under 35 U.S.C. 102(b) as being anticipated by the prior art (as set forth on pages 14-15 of the Office Action of 03/05/2009, in light of the amendments to the claims.

The Commissioner is hereby authorized to charge any fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 16-0877.

Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,



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